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14. ABSTRACT

This program is intended to establish the infrastructure to provide state-of-the art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project is intended to demonstrate whether 1) targeted radiation therapy with real time localization and tracking will allow use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and whether the use of such targeted therapy can occur within standard treatment times and thus feasible for routine clinical use, 2) whether the use of Vac-Lok® immobilization devices are necessary when patients are treated using the Calypso system, 3) whether Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy, 4) whether hypofractionated treatment plans which are more beam on time per fraction which may potentially account for more intra-fraction organ movement but allow for a shorter duration of treatment are feasible for routine clinical use with the Calypso system and 5) whether the localization of external beam radiation therapy (EBRT) can be improved to cancers of the liver.

15. SUBJECT TERMS
Calypso, Prostate, Intensity Modulated Radiation Therapy (IMRT), Planning Target Volume (PTV), Beacon Transponders

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Targeted Radiation Therapy for Cancer Initiative Annual Report

Introduction:

The full potential of radiation therapy has not been realized due to the inability to locate and track the tumor target continuously during the delivery of the radiation dose. Without the ability to accurately locate the tumor target at the time of dose delivery, more of the patient's healthy tissue is exposed to radiation, which may result in acute or chronic complications. The research studies and activities described will improve the techniques of modern radiation therapy and directly benefit the Departments of Defense and Veterans Affairs by: providing improved, state-of-the-art prostate cancer treatments to active-duty military personnel and veterans; continuing to investigate reduction of the number of daily radiation treatments required for each patient thereby reducing the cost of care and increasing treatment capacity within the military and veterans health care delivery system; enabling research to establish standards of care for targeted radiation therapy; establishing a DOD center of excellence in targeted radiation therapy and accelerating the development of the targeted radiation therapy platform to treat additional cancers that significantly affect service personnel and veterans, such as nonresectable cancers of the liver. The Calypso® 4D Localization System is utilized to track both inter-fraction and intra-fraction tumor movement in patients receiving radiation therapy for various malignancies. Improved tracking of tumors may lead to improved therapeutic outcomes. The Calypso® 4D Localization System is a FDA Class II device.

Body: Task Completion

Task 1. *Establishment of centers for targeted radiation therapy at MAMC and VAPSHCS with installation of the Calypso® 4D Localization System.*

Installation of the Calypso® 4D Localization System has successfully occurred at both MAMC and VAPSHCS.

The radiation team at MAMC continues to receive training and technical support of the system from Calypso as needed.

The VAPSHC team completed the final phase of Calypso training and treated their first (non-protocol) patient with the system simultaneously.

Task 2. *Treatment for prostate cancer with state-of-the art technology to allow real-time localization and continuous tracking of the tumor target.*

A total of 12 non-study patients who did not otherwise qualify for a protocol have been treated with the Calypso system at MAMC. Non-protocol patients have allowed the providers to gain further proficiency with the Calypso unit.

VAPSHCS has successfully completed treatment on one non-protocol patient. They too will continue to use the Calypso system on patients who do not otherwise qualify for a protocol.

Task 3. *Feasibility study with reduced planning treatment volume (PTV) margins and intensity modulated radiation therapy (IMRT) using targeted radiation therapy.*

In the last year, 3 new subjects have been enrolled in the study with Reduced PTV Margins at MAMC. A total of 11 have been enrolled to date; 1 is in the treatment phase, 8 are in the follow-up phase and 2 have completed the study.

Three amendments received MAMC IRB approval including: 1. MAJ Tinnel was added as an associate investigator. 2. Change of principal investigator from MAJ Brown to MAJ Macdonald and minor clarification to the protocol specifying who would be collecting the treatment times. 3. Dr. Wallner from the VA site was added as an associate investigator, and former AI, Dr. Martin was removed and added as the medical monitor. Continuing review for the protocol was approved by the MAMC IRB and granted from 20 July 2011 through 19 July 2012.

VAPSHCS is actively recruiting potential subjects for this trial. Although they have identified subjects who have met the inclusion criteria, these subjects opted to have brachytherapy instead of external beam radiation. Recruitment efforts continue and all patients deemed eligible are given the opportunity to participate.

In an effort to boost enrollment, we have collaborated with Brooke Army Medical Center. BAMC is currently treating patients using the Calypso system and has an abundant subject population that meet the protocol requirements. Now that we have received sponsor approval to add this site, we are in the process of getting BAMC IRB approval.

With the one (1) year no cost extension we were granted and by joining forces with BAMC, we feel optimistic that we will meet our accrual goals.

This study is expected to enroll a combined total of 20 subjects from both centers.

Task 4. *A Hypofractionated IMRT Therapy in Patients with Favorable Risk Prostate Cancer Using the Calypso® 4D Localization System: A Feasibility Study.*

We are awaiting the preliminary results from the RTOG 0415, which is a similar hypofractionated study (not using the Calypso System), to verify safety prior to proceeding with drafting the protocol manuscript. We are encouraged by the prospects of these study results as well as other recently published single-institution series on this subject, including the Italian study in high-risk patients published by G. Arcangeli et al in the September 2010 issue of the International Journal of Radiation Oncology * Biology * Physics. We expect to draft this protocol by early 2012.

This study is expected to enroll a combined total of 20 subjects from both centers.

Task 5. *A Randomized Study Comparing External Pelvic Immobilization to Limited Immobilization for the Treatment of Prostate Cancer with IMRT Using Real-Time, State -of-the-Art Motion Tracking with the Calypso® 4D Localization System.*

In the last year, 4 new subjects have been enrolled in this study at MAMC. A total of 7 have signed consent to date; 2 are in the treatment phase, 3 are in the follow-up phase, 1 completed the study and 1 withdrew consent prior to starting radiation treatment.

Two amendments received MAMC IRB approval including: 1. MAJ Tinnel was added as an associate investigator. 2. Change of principal investigator from MAJ Brown to MAJ Macdonald.

One deviation was reported and acknowledged by the IRB: Pt. #2003 who discontinued his Coumadin prior to having beacons implanted had a minimally elevated prothrombin time of 14.3 seconds which is outside the normal range of the upper limit of 14.2.; the test was repeated the next day prior to surgery and was found to be stable.

VAPSHCS received IRB and Research and Development Sub-Committee approvals. We are now awaiting final approval from the U.S. Army Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protections Office (HRPO).

We are encouraged that enrollment goals will be met, particularly now that we have the 1 year no cost extension in place.

This study is expected to enroll a combined total of 20 subjects from both centers.

Task 6. *Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study.*

Five new subjects have consented for this study at Madigan in the last year which includes 3 that were enrolled, 1 that withdrew consent prior to starting radiation therapy and 1 who is currently in the screening process. A total of 7 subjects have been enrolled in this trial to date and all have completed radiation therapy.

Three amendments received MAMC IRB approval including: 1. MAJ Tinnel was added as an associate investigator. 2. Change of principal investigator from MAJ Brown to MAJ Macdonald. 3. Revised consent form: changes to the consent form included correcting page 3, paragraph 1, from specifically stating 37 daily doses to 36-39 doses of radiation which better matches how this is stated in the protocol. The overall risk status remains greater than minimal.

One protocol deviation was reported to the IRB and acknowledged since the last quarterly report included the cone beam computed tomography (CBCT) was not functional on 03 June 2011 due to a circuit board problem, this affected subject #3009. Although this data will be unavailable for retrospective data analysis, the patient was set-up and treated appropriately using the Calypso system and his treatment was not compromised in any way.

VAPSHCS is awaiting regulatory approval. It has been put on the September 2011 IRB meeting agenda.

Since recruitment in this trial has occurred at an exceedingly fast rate, we submitted an amendment to the protocol requesting to increase enrollment from 10 to 20 subjects.

However, the MAMC IRB felt that the PI should conduct the interim analysis of data collected on the first 10 subjects and then, if an increase in enrollment is justified, re-submit the request, based on the data collected and analyzed. This analysis is currently underway.

This study is expected to enroll a combined total of 10 subjects from both centers.

Task 7. *Phase I/II trial of Real Time targeting of metastatic lesions in the liver with hypofractionated radiation therapy.*

Based on review of the current patient population, tt has been determined that it would be unlikely that we would be able to enroll enough subjects for any statistical value. Also, after numerous team meetings and discussions, the team does not believe there is not enough data available to support it.

We have a research meeting planned this fall and will be discussing the idea of pursuing a replacement protocol. Both cancers of the lung and spine have been topics of interest with the Calypso System as well as a new post-prostatectomy with reduced margins study which would be based on our initial results from the ongoing post-prostatectomy trial. We anticipate generating a viable plan for an alternate protocol by spring 2012.

Task 8. *Establish a center of excellence for targeted radiation therapy.*

The staff at MAMC have treated over 35 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant continues to facilitate continuing medical education for the staff at MAMC and VAPSHCS on image guided radiotherapy. Additional education materials and visits from other DOD/VA providers will be coordinated in upcoming years of the project.

We have identified a Radiation Oncologist resident who has expressed interest in doing a rotation at MAMC in the fall of 2012. The resident will learn advanced techniques of tumor targeting with the Calypso system and be given the opportunity to evaluate data and take part in writing scientific papers under the guidance of the MAMC physicians.

We have hosted two educational conferences/visiting professorships in the area of urology and radiation oncology in the last year. With the success of the last 2 symposiums, we have committed to making these events an annual occurrence. We believe these educational events promote our site as a “center of excellence in target radiation therapy” and encourage physicians in the community to seek our expertise.

We continue to collect information regarding problems/challenges encountered with Calypso as a "Lessons Learned Log" which identifies the problems encountered with possible causes and the techniques used to solve the problem.

Task 9: *Present findings of feasibility studies at professional conference.*

We anticipate presenting the initial findings of the Reduced PTV margins feasibility study at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012.

Problem Areas:

VAPSHCS – We have been disappointed in the very slow pace of protocol approval and patient accrual at VAPSHCS. Based on the current trend it seems unlikely that patient accrual at this site will substantially contribute to our research. On the other hand, by assisting VAPSHCS with their initial treatment of prostate cancer patients with the Calypso system, the goal of developing some level expertise in this area at VAPSHCS will likely be realized by the completion of the protocol. At present we are approaching this problem on two levels: (1) we continue to provide maximal support to VAPSHCS in accomplishing achievable milestones, and (2) we are attempting to ensure that funds directed to VAPSHCS are proportional to the progress they are making in accomplishing the Initiative's overall goals. We have considered the possibility of shifting resources away from VAPSHCS, including removing the Calypso unit there, but at this point such a move seems unproductive. We are excited to now be collaborating with BAMC, and expect this to be a fruitful partnership.

As stated in the last quarterly report, we do not plan on continuing effort toward the hypofractionated metastatic lesions study due to a lack of patient population and insufficient data to support it. We are interested in pursuing a post-prostatectomy reduced margin study which would be based on our initial results from the ongoing post-prostatectomy trial. We are also looking into the possibility of other research using the Calypso system as previously mentioned in this report and plan on sorting out the details and executing a plan.

Key Personnel Updates:

Dr. Dusten Macdonald is now the principal investigator of all the protocols at Madigan as well as the overall PI of the project. Dr. Brown has left the department and been removed from all of the protocols.

MAJ Tinnel was added as an associate investigator at MAMC.

At VAPSHCS Dr. Kent Wallner was added as an AI on the Reduced Margins study and Dr. Thomas Martin was removed as AI and added as medical monitor.

Key Research Accomplishments:

Enrolled 11 subjects on the Reduced PTV Margins protocol

Enrolled 7 subjects on the Immobilization protocol

Enrolled 7 subjects on the Post-prostatectomy protocol

Treated 13 non-study patients with Calypso

Analyzed data on 10 patients from the Reduced PTV Margins protocol and are completing an abstract on the subject of fecal continence. Abstract title: "Dose to the Muscles of Fecal Continence During Radiation Therapy for Prostate Cancer Using Calypso Localization: Small Reductions in Planning Target Volume (PTV) Margins Lead to Significant Tissue Sparing." We plan to present the results at an upcoming Genitourinary Oncology conference.

Reportable Outcomes: None at this time.

Conclusion: None at this time.

References: N/A

Appendices: N/A